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Review Article

Roles of Laboratory Animal Models in Zoonotic Diseases: A Review on Pathogenesis, Transmission, and Prevention Strategies

Seyed Mohsen Mousavi Fard[1], Ali Sarani[2*], Mohammad Manian[3], and Ali Hassanzadeh Teroujeni[4]

[1]Department of Clinical Sciences, Faculty of Veterinary Medicine, Islamic Azad University, Shoushtar Branch, Khuzestan, Iran
[2] Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Zabol, Zabol, Iran
[3] Department of Clinical Sciences, Faculty of Veterinary Medicine, Shiraz University, Shiraz, Iran
[4] Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran

Corresponding author: Ali Sarani, Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Zabol, Zabol, Iran. Email: alisarani@uoz.ac.ir

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ABSTRACT

Emerging zoonotic diseases have become an increasing concern for global health due to the rising incidence of pathogen transmission from animals to humans. The present study aimed to comprehensively synthesize the current knowledge on zoonotic disease outbreaks and transmission, with a specific focus on evaluating the role, applications, advantages, and limitations of laboratory animal models in this field. A peer-reviewed literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2000 and 2026, supplemented by earlier pivotal studies. The current study evaluated a range of models, including conventional, humanized, and transgenic mice, hamsters, ferrets, guinea pigs, rabbits, non-human primates, and emerging alternatives, focusing on their utility, strengths, and drawbacks for studying host-pathogen interactions, immune responses, tissue tropism, and disease progression. The present study underscored the importance of animal models in the preclinical assessment of antiviral agents, vaccines, monoclonal antibodies, and innovative therapeutic strategies. Recent outbreaks caused by pathogens such as SARS-CoV-2, Nipah virus, H5N1 influenza virus, Mpox virus, Ebola virus, Marburg virus, hantavirus, and Crimean-Congo hemorrhagic fever virus have highlighted the urgent necessity to enhance comprehension of zoonotic disease emergence and transmission. The current challenges included species-specific differences, translational limitations, reproducibility, and ethical considerations, as well as emerging alternatives such as organoids, organ-on-chip platforms, and computational modeling, all of which were addressed in the present findings. Integrating advanced animal models with One Health approaches can strengthen disease surveillance and accelerate therapeutic development.

1. Introduction

In recent years, emerging zoonotic diseases (EZDs) have become one of the biggest threats to the global public health community, given their increased prevalence, broad geographical range, and substantial health and economic impacts[1]. Zoonosis is any infectious disease that is naturally transmitted between animals and humans, and the majority of newly emerging infectious diseases are in this category[1]. The emergence of pathogens such as severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), Coronavirus Disease 2019 (COVID-19), Ebola virus disease, mpox, and highly pathogenic avian influenza viruses has demonstrated the detrimental effects of zoonotic pathogens on the healthcare system, the economy, and international trade[2].

The emergence of zoonotic pathogens is intimately linked to increasing interactions among human populations, domestic animals, wild animals, and the environment[1]. Many pathogens are silent, circulating in wildlife and crossing species boundaries to affect humans[3]. Once spillover occurs, pathogens may adapt to

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their new hosts, leading to localized outbreaks or, in some cases, global pandemics[3]. Consequently, preventing future zoonotic infections would require a comprehensive strategy that integrates human, animal, and environmental health, as articulated in the One Health concept. There are various interrelated environmental and anthropogenic factors behind the emergence and spread of zoonotic infections[1]. Climate change alters the distribution of wildlife reservoirs and disease vectors, increasing the likelihood of pathogen transmission in previously unaffected regions[4]. Rapid urbanization and population growth have intensified contact between humans and wildlife by encroaching on habitats, with deforestation and land-use changes further disturbing natural ecosystems and facilitating spillover events[5]. Moreover, legal and illegal trade in wildlife provides an opportunity for pathogens to spread among various animals, eventually reaching humans[6]. Increasing international travel and globalization allow emerging pathogens to spread rapidly across continents before effective containment measures can be implemented[6]. Agricultural intensification and high-density livestock production promote pathogen amplification and evolution by increasing contact among domestic animals, wildlife, and humans[7]. These factors have made zoonotic disease outbreaks frequent in recent decades.

Laboratory animal models are indispensable tools for investigating the pathogenesis, transmission, and control of EZDs[8]. Given that experiments involving humans are restricted by ethical considerations, laboratory animal models serve as effective systems for studying host-pathogen interactions, immune responses, tissue pathology, and disease progression[9]. In addition, laboratory animal models help in understanding the mechanism of adaptation and transmission of pathogens from one species to another[8]. Laboratory animals, including mice, hamsters, ferrets, guinea pigs, rabbits, and non-human primates, have been extensively used to study emerging zoonotic pathogens[10]. Genetic engineering techniques have enhanced the utility of laboratory animals by introducing transgenic and humanized animals that can simulate human susceptibility to infection[10]. Moreover, laboratory animal models remain essential for the preclinical evaluation of vaccines, antiviral drugs, monoclonal antibodies, and other therapeutic interventions[9]. Despite their limitations, including species-specific physiological differences and ethical concerns, laboratory animals remain the cornerstone of experimental infectious disease studies. Given the persistence of EZDs and the increased likelihood of future epidemics, it is crucial to understand the biology of these diseases and the experimental models used to study them. The present study aimed to summarize current knowledge on the pathogenesis, transmission, and prevention of EZDs, while emphasizing the pivotal role of laboratory animal models in investigations of zoonotic diseases.

2. Search criteria

The present narrative review was conducted through a literature search of PubMed, Scopus, Web of Science, and Google Scholar using combinations of keywords including EZDs, zoonotic pathogens, spillover, pathogenesis, transmission, laboratory animal models, animal models, vaccines, antiviral therapy, and One Health, along with pathogen-specific terms such as SARS-CoV-2, Nipah virus, H5N1, Mpox, Ebola virus, and Marburg virus. Peer-reviewed original research articles, review articles, and relevant reports by established international health organizations were considered. Recent literature from 2000 to 2026 was predominantly considered; however, some landmark publications from earlier periods were included when they provided seminal insights. Relevant publications were selected based on their scientific quality, alignment with the review's objectives, and contribution to understanding of zoonotic disease pathogenesis, transmission, animal models, therapeutic development, and prevention strategies. The retrieved evidence was thematically synthesized to provide a critical overview of EZDs and the current and future role of laboratory animal models.

3. Overview of emerging zoonotic diseases

3.1. Definition and classification

Emerging zoonoses are new or rapidly spreading diseases in a community caused by pathogens of animal origin that can be naturally transmitted to humans[1]. Complex interactions among environmental changes, pathogen evolution, and human activities often drive the emergence of zoonotic diseases[1]. The emergence of zoonotic diseases usually begins with the spillover of pathogens from their natural reservoirs into the human population, either directly or via intermediate hosts[11]. Depending on the pathogen's ability to adapt to human hosts, these events may result in sporadic infections, localized outbreaks, or widespread epidemics and pandemics[11]. Zoonotic pathogens comprise a wide variety of microorganisms, including viruses, bacteria, parasites, and fungi[12]. The pathogens differ considerably in their reservoirs, transmission routes, pathogenicity, and epidemic potential. While some pathogens are maintained primarily in wildlife populations, others circulate among domestic animals before infecting humans[13].

3.2. Major categories of emerging zoonotic diseases

Viruses constitute the largest proportion of emerging zoonotic pathogens and have caused most major outbreaks recorded over the past few decades[14]. The highly mutable nature of these pathogens, their ability to undergo genetic recombination and rapid adaptation to new hosts, facilitates the crossing of species barriers and establishment of human-to-human transmission[14]. Wildlife species, particularly bats, rodents, and birds, serve as important natural reservoirs for numerous zoonotic viruses[15]. Humans may become infected through direct contact with animals, contaminated food, vector-borne bites, or exposure to infected body fluids[11]. Several viral zoonoses, including coronaviruses, influenza viruses, filoviruses, and hantaviruses, have demonstrated

considerable pandemic potential and remain major priorities for global public health[16]. Emerging bacterial zoonoses continue to place a significant burden on human and veterinary medicine[1]. Among the common bacterial zoonoses are *Brucella* spp., *Leptospira* spp., *Salmonella* spp., *Campylobacter* spp., and *Bacillus* anthracis[17]. Increasing antibiotic resistance in zoonotic bacteria makes the treatment of such infections even more difficult[17]. Increasing antimicrobial resistance among zoonotic bacteria has further complicated disease management, underscoring the need for integrated surveillance and antimicrobial stewardship across the human and animal health sectors[18]. Parasitic zoonoses are caused by protozoa, helminths, and ectoparasites that can infect both humans and animals[19]. This transmission often involves food or water contamination, insects, or interaction with infected animals[20]. Important zoonotic parasites include *Toxoplasma gondii*, *Echinococcus* spp., Cryptosporidium spp., *Leishmania* spp., and *Trypanosoma* spp[21]. Although most parasitic infections are endemic diseases rather than epidemics, changes in the environment, travel, and climate change have led to the emergence of these infections in new geographic areas[21]. Although less frequently discussed than viral or bacterial infections, fungal zoonoses are increasingly recognized as important emerging diseases[22]. These infections are commonly transmitted through direct contact with infected animals or through environmental exposure to fungal spores[23]. Species such as *Microsporum*, *Trichophyton*, *Histoplasma capsulatum*, and *Sporothrix* spp. can cause zoonotic infections in humans[22]. An increased number of immunocompromised patients and environmental changes have led to an increase in certain types of zoonotic fungal infections[22].

3.2.1. Severe acute-respiratory-syndrome coronavirus 2

The emergence of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) in late 2019 led to the COVID-19 pandemic, which has been one of the deadliest global health threats in recent years[3]. Genetic evidence suggested a bat origin, although the precise intermediate host remains uncertain[24]. SARS-CoV-2 is known to spread via respiratory droplets and aerosols and demonstrates efficient human-to-human transmission[2]. Ongoing mutations have led to the development of various strains that differ in transmission rates, pathogenicity, and immune evasion abilities[24].

3.2.2. Nipah virus

Nipah virus is a highly pathogenic paramyxovirus maintained in fruit bats of the genus *Pteropus*[25]. Human beings may become infected through direct exposure to infected bats, consumption of contaminated foods such as date palm sap, or contact with domestic animals or other people[25]. Nipah virus causes severe respiratory disease and encephalitis with high case fatality rates. The Nipah virus is regarded as a priority pathogen by the World Health Organization (WHO) due to its epidemic capacity and lack of vaccines and antiviral medicines[26].

3.2.3. H5N1 influenza virus

Highly pathogenic avian influenza A(H5N1) virus primarily circulates among wild birds and domestic poultry; however, human infection from the virus has been reported in rare cases after exposure to infected birds[27]. Although sustained human-to-human transmission remains limited, the virus has significant pandemic potential due to its capacity for genetic reassortment and adaptation[28]. Frequent outbreaks in birds and occasional infections in mammals have led to fears of the emergence of more infectious strains[28].

3.2.4. Mpox virus

Mpox virus, formerly known as monkeypox virus, is an orthopoxvirus maintained in wildlife reservoirs, particularly rodents[29]. Traditionally restricted to Central and West Africa, the recent outbreak of Mpox was seen around the world starting in 2022[29]. Human transmission occurs through direct contact with infected animals, contaminated materials, or close physical contact with infected individuals[29]. The recent expansion of Mpox into non-endemic regions underscores the significance of global surveillance and rapid public health responses[30].

3.2.5. Hantavirus

Hantavirus is carried by rodents and causes hemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HCPS), depending on the specific species[31]. Human infection usually occurs through inhalation of aerosolized rodent excreta rather than through direct animal contact[31]. Changes in the environment, expansion of urban areas, and increased human intrusions into rodent habitats have been blamed for the persistence of hantavirus infections around the world[31].

3.2.6. Ebola virus

Ebola virus is a member of the *Filoviridae* family and causes severe hemorrhagic fever with high mortality rates[32]. Fruit bats have been identified as the most probable reservoirs, while other non-human primates have been shown to be the incidental hosts[32]. Infection in humans begins through contact with wild animals or body fluids and is transmitted from one individual to another[32]. Recurrent outbreaks in Africa continue to pose major public health challenges despite recent advances in vaccine development[32].

3.2.7. Marburg virus

The Marburg virus is related to the Ebola virus and causes hemorrhagic fever that results in high mortality rates[33]. Egyptian fruit bats are recognized as the principal natural reservoir[33]. There have been rare instances of outbreaks in sub-Saharan Africa; however, there have been some sporadic reports of cases being imported into other parts of the world[33]. The absence of licensed therapeutics and the potential for nosocomial

transmission underscore the need for continued investigations using appropriate experimental models[33].

3.2.8. Crimean-Congo hemorrhagic fever virus

Crimean-Congo hemorrhagic fever virus (CCHFV) is a tick-borne Nairovirus that is widespread in Africa, Asia, Eastern Europe, and the Middle East[34]. The CCHFV is maintained by complex cycles of transmission among *Hyalomma* ticks and different domestic and wild hosts[34]. Humans become infected through tick bites, contact with infected animal tissues, or exposure to contaminated blood during healthcare procedures[35]. Given its wide geographical distribution, high mortality rate, and lack of treatments, CCHFV continues to be one of the most important emerging zoonotic agents that require close monitoring and study[35].

4. Pathogenesis of emerging zoonotic diseases

The pathogenesis of EZDs is a complex process characterized by dynamic interactions between pathogens and hosts[1]. To be an efficient zoonotic pathogen, an agent must possess features that enable it to overcome biological barriers, including cross-species transmission, immune evasion, and adaptation to new hosts[1]. Disease severity depends not only on the pathogen's intrinsic characteristics but also on host susceptibility, immune status, genetic background, and environmental factors[4]. Therefore, the knowledge of pathogenesis is essential for preventive purposes and the development of therapeutic approaches and experimental animal models.

4.1. Host-pathogen interactions

The interactions between hosts and pathogens are the first and foremost point of zoonosis development[36]. Successful infection begins when a pathogen encounters susceptible host cells and attaches to specific cellular receptors through specialized surface molecules[37]. The affinity between host and pathogen can determine host susceptibility and affect the likelihood of spillover to other animals[38]. Mutations that improve receptor binding affinity may significantly enhance the ability of zoonotic pathogens to infect humans and establish sustained transmission[39]. After entering host cells, pathogens use diverse strategies to exploit cellular machinery for replication while evading host defense mechanisms[39]. Intracellular pathogens manipulate signaling pathways, block apoptosis, or affect antigen presentation to survive in the infected host[40]. On the other hand, extracellular pathogens use toxins, adhesion proteins, and enzymes to colonize tissues and spread throughout the host body[41]. Interactions between pathogen-derived molecules and host immunity throughout infection play a major role in determining the outcome, which can range from asymptomatic infection to systemic disease[41]. Host genetic variation also contributes to differences in susceptibility and clinical outcomes[42]. Genetic variations in immune genes, receptor expression, and inflammation can influence the pathogen's ability to enter the host, replicate, and cause disease[42].

4.2. Mechanisms of host adaptation

The hallmark of emergent zoonotic pathogens includes the ability to infect a novel host[4]. Species jumps by zoonotic pathogens require circumventing physiological, immunological, and ecological barriers to infection, which otherwise limit pathogens to their native reservoir[4]. Adaptation frequently occurs through the accumulation of genetic mutations, recombination, or genome reassortment, enabling pathogens to improve receptor recognition, replication efficiency, and immune evasion in the new host[43]. RNA viruses have high adaptability potential owing to their high mutation rates and error-prone replication processes[44]. This genetic flexibility allows rapid selection of variants with enhanced transmissibility or altered virulence under changing environmental or host conditions[44]. In contrast, bacterial and parasitic pathogens often adapt through horizontal gene transfer, acquisition of virulence determinants, antigenic variation, or metabolic flexibility[45]. Host adaptation is influenced not only by microbial evolution but also by ecological factors that increase opportunities for repeated exposure[37]. Interactions among wildlife, domestic animals, and humans can enable repeated infections and provide microbes with opportunities to evolve[37]. Adaptation to humans leads to efficient infection, which in turn enables human-to-human transmission, thus raising the possibility of epidemics and pandemics[37].

4.3. Immune responses and virulence factors

Laboratory models of infection have been useful in revealing information regarding the interplay between pathogen virulence and host immune response in zoonotic pathogens. Infection studies in laboratory animals have revealed that the course of disease depends on the balance between effective pathogen clearance and potentially harmful immune response activation. Innate responses, including interferon signaling, complement activation, phagocytic activity, and inflammatory cytokine production, constitute early defenses, whereas adaptive T- and B-cell responses contribute to pathogen clearance and immunological memory[46,47]. Mice, hamsters, ferrets, and non-human primate experimental infections suggest that a failure of early antiviral responses may allow for extensive pathogen replication. In contrast, excessive inflammatory responses can cause tissue injury and severe disease[46,47]. Animal models are important tools in studying the role of pathogen virulence factors in shaping host adaptation, tissue tropism, and disease progression. Viral proteins that mediate receptor interactions, cell entry, IFN antagonism, and immune evasion can be studied experimentally to assess their contributions to pathogenesis[48,49]. Similarly, bacterial, fungal, and parasitic virulence mechanisms can be investigated using controlled infection models[48]. It is

important to note that experimental adaptation investigations has shown that the interaction between pathogen genetics and host factors may alter a pathogen's virulence, transmission, and host range[22].

4.4. Disease progression and tissue tropism

The study of pathogen replication, tissue tropism, and host-response interactions is well facilitated by laboratory animal models of infection[4]. Laboratory infections of mice, hamsters, ferrets, and non-human primates are useful for monitoring pathogen dissemination and for determining target organs or cells within the infected organism. Receptor distribution, cellular compatibility, local immune responses, and tissue-specific physiological characteristics influence tissue tropism[50]. Comparative studies in animal models have demonstrated that differences in these factors can substantially affect viral replication, pathological lesions, and disease severity. In addition, experimental adaptation may alter pathogen tissue tropism, host range, and transmissibility, highlighting the importance of selecting animal models that faithfully reproduce human disease[50,51]. Additionally, adaptation in the experimental environment can result in changes in tissue tropism, host range, and ability to transmit the virus, emphasizing the importance of choosing appropriate animal models that mimic human diseases.

5. Transmission dynamics

Transmissions dynamics play an essential role in studying the emergence, persistence, and epidemic potential of zoonotic diseases[7,8]. Animal-to-human transmission (zoonotic spillover) is a major driver of disease emergence and occurs when pathogens maintained in animal reservoirs overcome interspecies barriers and infect susceptible hosts[36,52]. Wildlife populations, especially bats, rodents, birds, and non-human primates, may be considered essential reservoirs for many diseases, whereas domestic animals could serve as bridging hosts between people and animals[53]. Spillover may occur through direct contact, exposure to body fluids, aerosols, contaminated food or water, or arthropod vectors[53]. The pathogen load, frequency of host contact, environmental stability, and host susceptibility affect the probability of successful transmission[52]. Following spillover, some pathogens may acquire efficient human-to-human transmission, increasing their epidemic potential[54,55]. Environmental stability could help in spreading pathogens indirectly due to contamination of water, food, soil, or other environments[56-58]. Importantly, laboratory animal models provided controlled systems for investigating pathogen shedding, host susceptibility, transmission efficiency, and adaptation, thereby complementing field surveillance and improving understanding of zoonotic spillover mechanisms.

5.1. Reservoir hosts

Reservoir hosts are animal species in which pathogens naturally persist and replicate without causing substantial disease, thereby ensuring their long-term maintenance within ecosystems[59]. Reservoir hosts act as sources of infection and play an integral role in the epidemiology of EZDs[59]. Bats, rodents, wild birds, and some carnivores are among the most important reservoir hosts of wildlife identified to date[60]. The biological characteristics of reservoir hosts often facilitate pathogen persistence[59]. Long lifespans, social behavior, large population sizes, and extensive geographic distribution contribute to the continuous circulation of pathogens within these species[61]. Often, reservoir hosts have developed specific mechanisms of their immune response that allow them to carry persistent infections without experiencing any damage from them[59]. Identifying natural reservoirs is essential for understanding pathogen ecology and designing effective surveillance programs[62]. However, reservoir identification is difficult because many species of wildlife carry different types of microorganisms, and just because a pathogen is detected does not mean it is a reservoir[63]. The challenge of identifying reservoir hosts is that many species of wildlife carry different microorganisms; therefore, their presence is not evidence that they are reservoirs[63].

5.2. Intermediate hosts

Intermediate hosts, also known as amplification or bridging hosts, aid in the transmission of pathogens from reservoir hosts to humans[54]. Unlike reservoir hosts, intermediate hosts often develop clinical disease and may support extensive pathogen replication, thereby increasing opportunities for cross-species transmission[54]. Domestic animals often serve as intermediate hosts since they are in close contact with wildlife and humans[64]. Intermediate hosts may enhance zoonotic emergence by increasing pathogen abundance, promoting genetic adaptation, or bringing pathogens into closer contact with human populations[54]. In certain instances, pathogens may be subjected to evolutionary processes while in intermediate hosts that favor receptor binding, transmissibility and virulence prior to infection of humans[54]. Consequently, understanding the ecological role of intermediate hosts is critical for interrupting transmission chains and reducing spillover risk[54]. Nevertheless, the role of intermediate hosts varies considerably among pathogens[54]. There are some zoonoses that do not require intermediate hosts and are directly transmitted from wildlife to humans while others need complicated transmission chains that incorporate vectors, domestic and wildlife species[65].

5.3. Factors influencing spillover

Spillover is a multifactorial process arising from complex interactions among pathogens, hosts, and environmental factors rather than a single biological event[3]. For successful spillover to occur, a number of factors need to coincide, which are pathogen exposure, host susceptibility, ecological opportunity, and pathogen adaptation[11]. Environmental changes such as climate change, deforestation, habitat fragmentation, biodiversity

loss, and urban expansion have substantially increased contact between wildlife and human populations[5,16,43]. Such changes have destroyed natural ecosystems and created new ecological interfaces where spillover can take place. Likewise, globalization, international travel, wildlife trade, and intensified agriculture promote the rapid spread of pathogens across geographical areas[52]. In addition, microbial evolution plays a central role in spillover. Genetic mutations, recombination, reassortment, and horizontal gene transfer may enhance host receptor recognition, immune evasion, or replication efficiency, enabling pathogens to infect new host species[66]. At the same time, host-related factors including age, genetic susceptibility, nutritional status, immune competence, and underlying medical conditions influence individual vulnerability following pathogen exposure[66].

6. Laboratory animal models in zoonotic disease investigations

Animal models used in laboratory experiments are an extremely important resource in the study of zoonoses, serving as a means of investigating pathogen biology, host reaction, pathogenesis, and the effects of vaccines and medications[67]. Since there is a range of zoonotic pathogens with complicated pathogen transmission cycles and pathogenic mechanisms, *in vivo* experiments continue to be extremely necessary for studying disease mechanisms that cannot be replicated by other methods such as cell cultures or computer simulation[67]. Although advances in organoid and organ-on-chip technologies have expanded experimental capabilities, animal models remain the gold standard for studying host-pathogen interactions in a physiologically relevant context[68]. Selecting an appropriate animal model requires careful consideration of the biological characteristics of both the pathogen and the host. The selection of an animal model is highly dependent on the biology of the pathogen and the host (Table 1).

6.1. Mouse

Mice are the most widely used laboratory animals for studies of infectious diseases thanks to their well-established genetics, rapid reproductive cycles, low maintenance costs, and abundance of molecular and immunological tools. However, conventional strains such as BALB/c and C57BL/6 often fail to support infection by emerging zoonotic pathogens due to species-specific differences in receptors and immune responses[69]. To overcome the limitations mentioned above, humanized mice, which are the result of inoculating human immune cells and tissue into immunodeficient recipients, were created, enabling the investigation of human immune responses to zoonotic pathogens and potential antiviral medicines. However, these mice are technically demanding, expensive, and variable in reconstitution[70]. In addition, there are transgenic mice with human gene expression, which is useful in studying zoonoses because of the ability to examine viral infection, progression of the disease, immune reaction, and test vaccines and antivirals on them[71,72]. Conventional mice are important for basic studies, while humanized and transgenic models expand research on human pathogens and improve preclinical investigations of zoonotic relevance[69].

6.2. Hamster

Hamsters, particularly the Syrian hamster (*Mesocricetus auratus*), have become one of the most valuable small-animal models for studying emerging zoonotic viral diseases because they are naturally susceptible to many human pathogens without extensive genetic modification. Hamsters often exhibit pathology similar to human diseases, making them very useful for translational studies[73]. A major advantage is their ability to support efficient viral replication in both the upper and lower respiratory tracts, making them indispensable for studying respiratory pathogens such as SARS-CoV-2 and influenza viruses[74,75]. The infected hamsters display weight loss, inflammatory responses in the lungs, pneumonia caused by viruses, and immune responses which very much resemble the disease in humans[74,75]. These features have established hamsters as a preferred model for investigating viral pathogenesis, transmission dynamics, immune responses, and post-infection pulmonary pathology. Additionally, hamsters are commonly employed in the pre-clinical testing of vaccines, antiviral drugs, and monoclonal antibody treatments because of the ease of housing them in large numbers and their moderate cost[73]. Nonetheless, hamster models are not without flaws, such as having far fewer immunologic agents specific to the species compared to mice, thus making mechanistic studies difficult[76].

6.3. Ferret

Ferrets (*Mustela putorius furo*) are considered among the most valuable animals for studying respiratory zoonotic viruses because of the strong anatomical and physiological similarities between ferret and human respiratory systems. This similarity in respiratory systems includes similarities in airway architecture, receptor distribution, and viral replication patterns, enabling them to exhibit many facets of naturally acquired respiratory infections[77]. Ferrets have been extensively used to study influenza viruses, including highly pathogenic avian influenza A(H5N1), as well as SARS-CoV and SARS-CoV-2. In contrast to many other rodents, ferrets easily transmit respiratory viruses to each other through direct contact and droplets of breathing, which makes them useful in the study of transmission of these viruses[78]. Since ferrets serve as an excellent model for studying respiratory infection, these animals are extensively used to assess viral virulence, infection transmissibility, and the efficacy of public health measures, vaccines, and antivirals prior to conducting clinical trials[78]. Nonetheless, several obstacles to conducting ferret studies exist, including the

high cost of acquiring the animals, specific housing requirements, and limited availability of immunological reagents, all of which constrain the use of ferrets in investigations. Relatively few genetically modified ferret strains are available compared with mouse models, reducing opportunities for detailed molecular investigations.

6.4. Guinea pig

Guinea pigs (*Cavia porcellus*) play a crucial role in studies of zoonotic diseases due to their susceptibility to different bacterial and viral pathogens and their ease of maintenance in laboratory settings. Guinea pigs have proved valuable models for the study of diseases such as tuberculosis, leptospirosis, brucellosis, and other bacterial zoonoses. More recently, guinea pigs have become objects of study for specific viral hemorrhagic fever and respiratory disease viruses[79]. A notable advantage of guinea pigs is their ability to develop pathological lesions that resemble certain aspects of human disease, particularly in pulmonary infections. Guinea pigs are now essential for evaluating pathogen spread, inflammation, and vaccine effectiveness. In some virus infection models, guinea pigs can harbor virus replication without much genetic engineering, thus enabling the investigation of disease development in relatively natural conditions[80]. Moreover, guinea pigs serve as practical models for pharmacological and toxicological evaluations due to their manageable size and straightforward husbandry requirements, and their use in vaccine development has contributed to the preclinical evaluation of several experimental immunization strategies[80].

6.5. Rabbit

Rabbits (*Oryctolagus cuniculus*) have long been used in biomedical research and continue to provide valuable experimental systems for selected zoonotic diseases[81,82]. The large body size of these animals, compared with rodents, allows blood sampling, more complex imaging, and observation of physiological parameters without interfering with the experiment[81]. The rabbit models have been used in studies of bacterial infections such as anthrax, tularemia, and Q fever, as well as in investigations of some viral diseases[83]. Rabbits show clinical symptoms and pathological changes similar to those in humans, thereby enabling study of the disease course, vascular lesions, and tissue damage 83. Rabbits have also been extensively used to evaluate vaccine safety, immunogenicity, and antibody production because of their robust humoral immune responses[84]. Another strength of rabbits is their suitability for surgical experiments and multiple tissue sampling, which allow for stage-specific pathology analysis of the infection process[82]. Their intermediate body size also supports pharmacokinetic studies that require repeated administration and sampling[82]. Despite these strengths, rabbits are less commonly used than mice or hamsters because of higher maintenance costs, longer reproductive cycles, and more limited genetic resources[85]. Susceptibility differences among species further reduce the applicability of rabbits to EZD models[82].

6.6. Non-human primates

Non-human primates (NHPs), including macaques, green monkeys, baboons, and marmosets, serve as the most relevant models for emerging zoonotic pathogens because of their close genetic and immunological ties to humans. This similarity enables NHPs to exhibit human-like clinical signs, immune responses, and multiorgan pathology. Consequently, they are vital for studying high-impact viruses such as SARS-CoV-2, Ebola, Marburg, and Nipah, as well as for identifying protective immunity markers and validating vaccines before human clinical trials trials[86,87]. Their compatibility with advanced techniques such as single-cell transcriptomics and imaging offers exceptional precision; however, high costs, specialized housing, biosafety requirements, and ethical considerations restrict their use. Therefore, NHPs are designated for late-stage studies when smaller models are insufficient insufficient[86]. Overall, together with hamsters, ferrets, guinea pigs, and rabbits, NHPs offer complementary advantages, and model selection depends on the pathogen, study goals, and the balance among translational value, feasibility, and ethics[85].

6.7. Alternative animals

While rodents and NHPs represent the major zoonotic animal models, other models such as tree shrews, cotton rats, fruit bats, and zebrafish are being considered due to their unique features, their ability to address certain questions, and their adherence to the 3Rs policy[88]. Tree shrews are evolutionarily closer to primates than to rodents, are susceptible to influenza, hepatitis, and coronaviruses, and offer an intermediate model at lower cost than NHPs. However, standardized reagents and genetic approaches for studying tree shrews are lacking[89]. Cotton rats are naturally susceptible to human pathogens such as influenza and RSV, lack adaptation to these viruses, and develop severe pulmonary inflammation. However, cotton rats, as animal models, lack immunological and genetic tools[90]. The fruit bat is a natural reservoir host for several highly pathogenic viruses, including Nipah, Hendra, Ebola, and Marburg. However, there are various limitations associated with their use, including housing, biosafety concerns, and ethical considerations[91]. Zebrafish offer rapid reproduction, genetic tractability, and optical transparency for real-time imaging of innate immunity and infection dynamics, though they are physiologically distant from mammals and unsuitable for respiratory studies[92]. However, the physiological differences from mammals, as well as their inability to serve in respiratory investigations, limit the use of these animals.

Table 1. Comparative characteristics of laboratory animals used in emerging zoonotic disease studies

Animal model	Major advantages	Principal limitations	Representative zoonotic pathogens	Primary study applications
Conventional mice	Low cost, rapid breeding, abundant immunological tools, extensive genetic resources	Limited susceptibility to several human pathogens	Influenza viruses, *Leptospira*, *Brucella*, *Toxoplasma*	Immunology, pathogenesis, vaccine and drug evaluation
Humanized mice	Human immune system components, improved translational relevance	Expensive, technically demanding, incomplete immune reconstitution	SARS-CoV-2, HIV-related study, emerging viral infections	Human immune responses, monoclonal antibodies, vaccine development
Transgenic mice	Expression of human receptors, precise genetic manipulation	Development is time-consuming and costly	SARS-CoV-2, MERS-CoV, Nipah virus	Receptor biology, pathogenesis, antiviral testing
Syrian hamster	Natural susceptibility, human-like respiratory disease	Limited molecular and immunological reagents	SARS-CoV-2, influenza viruses, Nipah virus	Respiratory pathology, transmission, therapeutics
Ferret	Human-like respiratory physiology, efficient respiratory transmission	High maintenance cost, limited genetic tools	Influenza viruses, SARS-CoV-2	Transmission studies, vaccine evaluation
Guinea pig	Susceptibility to bacterial pathogens, moderate maintenance cost	Few transgenic models, limited reagents	*Brucella*, *Leptospira*, influenza viruses	Bacterial pathogenesis, vaccine studies
Rabbit	Larger body size, strong antibody responses, repeated sampling	Longer breeding cycle, limited genetic resources	Anthrax, tularemia, Q fever	Immunogenicity, pathology, pharmacokinetics
Non-human primates	Closest physiological similarity to humans, highly translational	Ethical concerns, very high cost, specialized facilities	SARS-CoV-2, Ebola, Marburg, Nipah virus	Advanced pathogenesis, vaccine validation, therapeutic development
Tree shrew	Genetic similarity to primates, suitable for respiratory and neurological studies	Limited laboratory resources	Influenza viruses, coronaviruses	Host adaptation, respiratory infections
Cotton rat	Natural susceptibility to respiratory viruses	Limited molecular tools	Influenza viruses, RSV	Respiratory pathogenesis, vaccine evaluation
Fruit bat	Natural reservoir host, reservoir biology studies	Difficult husbandry, biosafety concerns	Ebola, Marburg, Nipah, Hendra viruses	Reservoir ecology, viral persistence, spillover mechanisms
Zebrafish	Optical transparency, rapid genetics, high-throughput screening	Limited mammalian physiological similarity	Selected bacterial and fungal pathogens	Innate immunity, host–pathogen interactions, drug screening

HIV: Human immunodeficiency virus, RSV: Respiratory syncytial virus, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, MERS-CoV: Middle East respiratory syndrome–related coronavirus

7. Contributions of animal models to understanding disease pathogenesis

Animal studies have furthered knowledge regarding zoonotic infections by allowing reproduction of human diseases in a controlled environment to understand viral replication, immune response, tissue damage, and disease progression and to test therapies and biomarkers[93]. For viral replication, models such as mice, hamsters, ferrets, and NHPs have helped identify target cells, track viral dissemination, and evaluate shedding patterns, guiding antiviral development[71,78]. Regarding immune mechanisms, animal studies have indicated roles for interferons, macrophages, T lymphocytes, and antibodies, with genetically modified mice providing valuable insights into how specific immune pathways can be linked to either resistance or susceptibility to disease[94]. For organ-specific pathology, these models have enabled systematic examination of lesions in the lungs, liver, brain, and other organs, revealing mechanisms of tissue injury and multiorgan involvement that are difficult to study in humans[95]. Animal models have demonstrated that excessive cytokine production causes serious disease through endothelial damage and vascular leakage, providing evidence for the use of anti-inflammatory medicines[96]. In addition, animal studies are increasingly being used for studying chronic effects, such as fib[96]. Moreover, animal models are increasingly used to investigate long-term sequelae, such as fibrosis, neurological impairment, and immune dysregulation after recovery, thereby aiding the development of interventions to prevent chronic damage[97]. Animal models have helped bridge the gap between the virus's biological properties and the host's immune response, with this knowledge vital for the development of vaccines, antiviral medicines, and other therapeutic agents.

8. Animal models for therapeutic and vaccine development

Animal models play a key role in the preclinical assessment of potential vaccines and therapeutics against EZDs through providing controlled settings to analyze safety, effectiveness, pharmacokinetics, and immune response prior to human trials[98]. For the evaluation of antiviral medicines, small animals such as mice and hamsters are utilized for preliminary screening. In contrast, non-human primates validate promising candidates through studies of dosing, toxicity, and therapeutic efficacy[69,87]. Animal models such as mice, hamsters, ferrets, and NHPs assist in studying the

effectiveness of vaccination by assessing the generation of antibodies, cell-mediated immune response, and protection against challenge, including virus infection and transmission[85,87]. Furthermore, animal models have been invaluable for passive immunotherapy, allowing assessment of the timing, dosage, and protective effects of antibody transfer, particularly during outbreaks when other options are limited[94]. For monoclonal antibodies, animal models enable the identification of neutralizing antibodies, the evaluation of antiviral activity, and the testing of combination therapies against viral variants[100]. Additionally, Animal models have been useful for novel therapeutic modalities such as host-targeted therapies, RNA therapies, genome editing, and nanotechnology[101].

9. Prevention and control strategies

Prevention of EZDs requires concerted initiatives that integrate human, animal, and environmental health through a multidisciplinary approach, including early detection and intervention, with laboratory animal models still used in the development of preventive measures. The One Health approach fosters collaboration among physicians, veterinarians, ecologists, and public health professionals to improve surveillance and risk assessment[102]. Surveillance systems that integrate human, veterinary, and environmental components will enable rapid pathogen detection and early intervention before the disease spreads widely[103]. Vaccination remains a key preventive tool for humans, domestic animals, and wildlife, with animal models playing a crucial role in preclinical evaluation of vaccine safety and efficacy[104]. Biosecurity measures such as proper farm management, infection control, safe animal handling, and sanitation help reduce transmission at the human-animal interface[105]. Wildlife surveillance is important since wildlife form the main reservoirs of many emerging infectious diseases, while ecologic surveillance is useful in evaluating the chances of disease spillover to humans and preventing the problem[13,4]. Preparedness in public health involves enhancing laboratory capacity, diagnostic techniques, emergency planning, and public education[43]. Effective prevention depends on an integrated strategy combining surveillance, vaccination, biosecurity, wildlife monitoring, and coordinated action within the One Health framework.

10. Conclusion

Emerging zoonotic diseases pose significant threats to global health due to increasing human–animal interactions, environmental changes, and pathogen evolution. Understanding pathogen transmission, host adaptation, and disease pathogenesis is essential for the development of effective preventive and therapeutic strategies. Laboratory animals play a crucial role in understanding host–pathogen interactions, exploring immune responses, and evaluating the safety and efficacy of vaccines and new therapies. Although no single animal model fully reproduces human disease, the complementary use of conventional, genetically engineered, and alternative models has substantially advanced translational investigations. Emerging technologies, including organoids, organ-on-chip systems, and computational approaches, are expected to enhance rather than replace animal-based studies. Future studies should integrate advanced experimental models with multidisciplinary One Health approaches to improve disease surveillance and accelerate therapeutic development for emerging zoonotic threats.

Declarations

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Availability of data and materials

As this study is a narrative review based on previously published literature, no new datasets were generated or analyzed. The references supporting this review are available within the article, and additional information can be provided by the corresponding author upon reasonable request.

Authors' contributions

Seyed Mohsen Mousavi Fard contributed to study conception, literature search, study selection, and manuscript drafting. Ali Sarani contributed to the review framework, critical interpretation, supervision, and manuscript revision. Mohammad Manian contributed to the literature search, study selection, data organization, and manuscript drafting. Ali Hassanzadeh Teroujeni contributed to critical analysis, scientific review, and manuscript revision. All authors read and approved the final edition and agreed to be accountable for the content of the manuscript.

Competing interests

The authors have declared that no competing interests exist.

Ethical consideration

During manuscript preparation, the authors used Gemini (an advanced language model developed by Google) solely for language polishing and improving structural flow. After using this tool, the authors thoroughly reviewed, verified, and edited the suggested content to ensure scientific accuracy and take full responsibility for the final integrity and factual correctness of the peer-reviewed text. The authors take full responsibility for the data in the present study, which were originally collected and analyzed by the authors before submission and during the peer-review process.

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References

1. Rahman MT, Sobur MA, Islam MS, Ievy S, Hossain MJ, El Zowalaty ME, et al. Zoonotic diseases: Etiology, impact, and control. Microorganisms. 2020; 8(9): 1405. DOI: 10.3390/microorganisms8091405
2. Lombardi AF, Afsahi AM, Gupta A, and Gholamrezanezhad A. Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), influenza, and COVID-19, beyond the lungs: A review article. Radiol Med. 2021; 126(4): 561-569. DOI: 10.1007/s11547-020-01311-x
3. Bhatia B, Sonar S, Khan S, and Bhattacharya J. Pandemic-proofing: Intercepting zoonotic spillover events. Pathogens. 2024; 13(12): 1067. DOI: 10.3390/pathogens13121067
4. Wilcox BA, and Gubler DJ. Disease ecology and the global emergence of zoonotic pathogens. Environ Health Prev Med. 2005; 10(5): 263-272. DOI: 10.1265/ehpm.10.263
5. Hassell JM, Begon M, Ward MJ, and Fèvre EM. Urbanization and disease emergence: dynamics at the wildlife-livestock-human interface. Trends Ecol Evol. 2017; 32(1): 55-67. DOI: 10.1016/j.tree.2016.09.012
6. Travis DA, Watson RP, and Tauer A. The spread of pathogens through trade in wildlife. Sci Tech Rev. 2011; 30(1): 219-231. DOI: 10.20506/rst.30.1.2035
7. Esposito MM, Turku S, Lehrfield L, and Shoman A. The impact of human activities on zoonotic infection transmissions. Animals. 2023; 13(10): 1646. DOI: 10.3390/ani13101646
8. Kane Y, Wong G, and Gao GF. Animal models, zoonotic reservoirs, and cross-species transmission of emerging human-infecting coronaviruses. Annu Rev Anim Biosci. 2023; 11(1): 1-31. DOI: 10.1146/annurev-animal-020420-025011
9. Pradhan B, and Satapathy T. Experimental animal models of human depression: Understanding the mechanism of anti-depressant agents. J Lab Anim Res. 2024; 3(2): 6-16. DOI: 10.58803/jlar.v3i2.40
10. Farah IO, Ngotho M, Kariuki T, Jeneby N, Maina N, Kagira JM, et al. Animal models of tropical parasitic diseases. Handbook of laboratory animal science. 3rd ed. Florida: CRC Press; 2004. p. 169-223. Available at: https://www.cabidigitallibrary.org/doi/abs/10.5555/20053033054
11. Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, et al. Pathways to zoonotic spillover. Nat Rev Microbiol. 2017; 15(8): 502-510. DOI: 10.1038/nrmicro.2017.45
12. World health organization (WHO). Zoonoses. WHO, 2020. Available at: https://www.who.int/news-room/fact-sheets/detail/zoonoses
13. Karesh WB, Dobson A, Lloyd-Smith JO, Lubroth J, Dixon MA, Bennett M, et al. Ecology of zoonoses: Natural and unnatural histories. Lancet. 2012; 380(9857): 1936-1945. DOI: 10.1016/S0140-6736(12)61678-X
14. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, et al. Global trends in emerging infectious diseases. Nature. 2008; 451(7181): 990-993. DOI: 10.1038/nature06536
15. Letko M, Seifert SN, Olival KJ, Plowright RK, and Munster VJ. Bat-borne virus diversity, spillover and emergence. Nat Rev Microbiol. 2020; 18(8): 461-471. DOI: 10.1038/s41579-020-0394-z
16. Letko M, Plowright RK, and Munster VJ. Ecology, evolution and spillover of coronaviruses from bats. Nat Rev Microbiol. 2022; 20(5): 299-314. DOI: 10.1038/s41579-021-00652-2
17. Hakimi H, Sarani A, Takeda M, Kaneko O, and Asada M. Epidemiology, risk factors, and co-infection of vector-borne pathogens in goats from Sistan and Baluchestan province, Iran. PLoS One. 2019; 14(6): e0218609. DOI: 10.1371/journal.pone.0218609
18. Cantas L, and Suer K. The important bacterial zoonoses in "One Health" concept. Front Public Health. 2014; 2: 144. DOI: 10.3389/fpubh.2014.00144
19. Shahrokhi A, Moradpour N, Siahsarvie R, and Borji H. An investigation of potentially zoonotic helminth parasites of Allactaga elater in Sarakhs, Iran. J Lab Anim Res. 2022; 1(1): 8-13. DOI: 10.58803/jlar.v1i1.7
20. Jahantigh FF, Rasekh M, Ganjali M, and Sarani A. Seroprevalence of *Toxoplasma gondii* infection among pregnant women and small ruminant populations in Sistan region, Iran. Iran J Vet Med. 2020; 14(3): 215-224. DOI: 10.22059/ijvm.2020.294216.1005048
21. Kaminsky R, and Mäser P. Global impact of parasitic infections and the importance of parasite control. Front Parasitol. 2025; 4: 1546195. DOI: 10.3389/fpara.2025.1546195
22. Friedman DZ, and Schwartz IS. Emerging fungal infections: New patients, new patterns, and new pathogens. J Fungi. 2019; 5(3): 67. DOI: 10.3390/jof5030067
23. Carpouron JE, de Hoog S, Gentekaki E, and Hyde KD. Emerging animal-associated fungal diseases. J Fungi. 2022; 8(6): 611. DOI: 10.3390/jof8060611
24. Hon CC, Lam TY, Shi ZL, Drummond AJ, Yip CW, Zeng F, et al. Evidence of the recombinant origin of a bat severe acute respiratory syndrome (SARS)-like coronavirus and its implications on the direct ancestor of SARS coronavirus. J Virol. 2008; 82(4): 1819-1826. DOI: 10.1128/jvi.01926-07
25. Singh RK, Dhama K, Chakraborty S, Tiwari R, Natesan S, Khandia R, et al. Nipah virus: Epidemiology, pathology, immunobiology and advances in diagnosis, vaccine designing and control strategies – a comprehensive review. Vet Q. 2019; 39(1): 26-55. DOI: 10.1080/01652176.2019.1580827
26. Bruno L, Nappo MA, Ferrari L, Di Lecce R, Guarnieri C, Cantoni AM, et al. Nipah virus disease: Epidemiological, clinical, diagnostic and legislative aspects of this unpredictable emerging zoonosis. Animals. 2022; 13(1): 159. DOI: 10.3390/ani13010159
27. Nuñez IA, and Ross TM. A review of H5Nx avian influenza viruses. Ther Adv Vaccines Immunother. 2019; 7: 2515135518821625. DOI: 10.1177/2515135518821625
28. Van Kerkhove MD, Mumford E, Mounts AW, Bresee J, Ly S, Bridges CB, et al. Highly pathogenic avian influenza (H5N1): Pathways of exposure at the animal–human interface, a systematic review. PLoS One. 2011; 6(1): e14582. DOI: 10.1371/journal.pone.0014582
29. Falendysz EA, Lopera JG, Rocke TE, and Osorio JE. Monkeypox virus in animals: Current knowledge of viral transmission and pathogenesis in wild animal reservoirs and captive animal models. Viruses. 2023; 15(4): 905. DOI: 10.3390/v15040905
30. Srivastava S, Kumar S, Jain S, Mohanty A, Thapa N, Poudel P, et al. The global monkeypox (Mpox) outbreak: a comprehensive review. Vaccines. 2023; 11(6): 1093. DOI: 10.3390/vaccines11061093
31. Chen RX, Gong HY, Wang X, Sun MH, Ji YF, Tan SM, et al. Zoonotic *Hantaviridae* with global public health significance. Viruses. 2023; 15(8): 1705. DOI: 10.3390/v15081705
32. Nicastri E, Kobinger G, Vairo F, Montaldo C, Mboera LE, Ansunama R, et al. Ebola virus disease: Epidemiology, clinical features, management, and prevention. Infect Dis Clin. 2019; 33(4): 953-976. DOI: 10.1016/j.idc.2019.08.005
33. Woolsey C, and Geisbert TW. Marburg virus disease: A comprehensive review. Clin Microbiol Rev. 2026; e00097-23. DOI: 10.1128/cmr.00097-23
34. Shahhosseini N, Wong G, Babuadze G, Camp JV, Ergonul O, Kobinger GP, et al. Crimean-Congo hemorrhagic fever virus in Asia, Africa and Europe. Microorganisms. 2021; 9(9): 1907. DOI: 10.3390/microorganisms9091907
35. Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J Med Entomol. 1979; 15(4): 307-417. DOI: 10.1093/jmedent/15.4.307
36. Escudero-Pérez B, Lalande A, Mathieu C, and Lawrence P. Host–pathogen interactions influencing zoonotic spillover potential and transmission in humans. Viruses. 2023; 15(3): 599. DOI: 10.3390/v15030599
37. Begeman L, Van Riel D, Koopmans MP, and Kuiken T. The pathogenesis of zoonotic viral infections: Lessons learned by studying reservoir hosts. Front Microbiol. 2023; 14: 1151524. DOI: 10.3389/fmicb.2023.1151524
38. Singh BB, Ward MP, and Dhand NK. Host characteristics and their influence on zoonosis, disease emergence and multi-host pathogenicity. One Health. 2023; 17: 100596. DOI: 10.1016/j.onehlt.2023.100596
39. Ou J, Zhou Z, Dai R, Zhang J, Zhao S, Wu X, et al. V367F mutation in SARS-CoV-2 spike RBD emerging during the early transmission phase enhances viral infectivity through increased human ACE2 receptor binding affinity. J Virol. 2021; 95(16): e00617-21. DOI: 10.1128/JVI.00617-21
40. Thakur A, Mikkelsen H, and Jungersen G. Intracellular pathogens: Host immunity and microbial persistence strategies. J Immunol Res. 2019; 2019(1): 1356540. DOI: 10.1155/2019/1356540
41. Pizarro-Cerdá J, and Cossart P. Bacterial adhesion and entry into host cells. Cell. 2006; 124(4): 715-727. DOI: 10.1016/j.cell.2006.02.012
42. Kwok AJ, Mentzer A, and Knight JC. Host genetics and infectious disease: New tools, insights and translational opportunities. Nat Rev

Genet. 2021; 22(3): 137-153. DOI: 10.1038/s41576-020-00297-6
43. Plowright RK, Ahmed AN, Coulson T, Crowther TW, Ejotre I, Faust CL, et al. Ecological countermeasures to prevent pathogen spillover and subsequent pandemics. Nat Commun. 2024; 15(1): 2577. DOI: 10.1038/s41467-024-46151-9
44. Dolan PT, Whitfield ZJ, and Andino R. Mechanisms and concepts in RNA virus population dynamics and evolution. Annu Rev Virol. 2018; 5(1): 69-92. DOI: 10.1146/annurev-virology-101416-041718
45. Chen Y, Wu X, Xu C, Huang J, Zhang L, Qiu P, et al. Pathogen virulence genes: advances, challenges and future directions in infectious disease research. Int J Mol Med. 2025; 56(5): 173. DOI: 10.3892/ijmm.2025.5614
46. Purushotham JN, Lutz HL, Parker E, and Andersen KG. Immunological drivers of zoonotic virus emergence, evolution, and endemicity. Immunity. 2025; 58(4): 784-796. DOI: 10.1016/j.immuni.2025.03.014
47. Mabbott NA. The influence of parasite infections on host immunity to co-infection with other pathogens. Front Immunol. 2018; 9: 2579. DOI: 10.3389/fimmu.2018.02579
48. Casadevall A, and Pirofski LA. Virulence factors and their mechanisms of action: The view from a damage–response framework. J Water Health. 2009; 7(S1): S2-S18. DOI: 10.2166/wh.2009.036
49. Kitamoto S, Nagao-Kitamoto H, Kuffa P, and Kamada N. Regulation of virulence: the rise and fall of gastrointestinal pathogens. J Gastroenterol. 2016; 51(3): 195-205. DOI: 10.1007/s00535-015-1140-6
50. McCall LI, Siqueira-Neto JL, and McKerrow JH. Location, location, location: Five facts about tissue tropism and pathogenesis. PLoS Pathog. 2016; 12(5): e1005519. DOI: 10.1371/journal.ppat.1005519
51. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: Underestimated opportunistic pathogens of the central nervous system? Viruses. 2019; 12(1): 14. DOI: 10.3390/v12010014
52. Alexander KA, Carlson CJ, Lewis BL, Getz WM, Marathe MV, Eubank SG, et al. The ecology of pathogen spillover and disease emergence at the human-wildlife-environment interface. In: Hurst CJ, editor. The connections between ecology and infectious disease. Cham: Springer International Publishing; 2018. p. 267-298. DOI: 10.1007/978-3-319-92373-4_8
53. Greger M. The human/animal interface: Emergence and resurgence of zoonotic infectious diseases. Crit Rev Microbiol. 2007; 33(4): 243-299. DOI: 10.1080/10408410701647594
54. Parrish CR, Holmes EC, Morens DM, Park EC, Burke DS, Calisher CH, et al. Cross-species virus transmission and the emergence of new epidemic diseases. Microbiol Mol Biol Rev. 2008; 72(3): 457-470. DOI: 10.1128/MMBR.00004-08
55. Straif-Bourgeois S, Tonzel JL, Kretzschmar M, and Ratard R. Infectious disease epidemiology. In: Ahrens W, Pigeot I, editors. Handbook of epidemiology. 2nd ed. New York, NY: Springer New York; 2023. p. 1-79. DOI: 10.1007/978-1-4614-6625-3_34-1
56. Friedman R, and Perl TM. Outbreaks of emerging and re-emerging infections and their management in healthcare settings. Infect Dis Clin. 2026; 40(2): 317-342. DOI: 10.1016/j.idc.2026.02.001
57. Rees EM, Minter A, Edmunds WJ, Lau CL, Kucharski AJ, and Lowe R. Transmission modelling of environmentally persistent zoonotic diseases: A systematic review. Lancet Planet Health. 2021; 5(7): E466-E478. DOI: 10.1016/S2542-5196(21)00137-6
58. Turner WC, Kamath PL, Van Heerden H, Huang YH, Barandongo ZR, Bruce SA, et al. The roles of environmental variation and parasite survival in virulence–transmission relationships. R Soc Open Sci. 2021; 8(6): 210088. DOI: 10.1098/rsos.210088
59. Dobson A. Population dynamics of pathogens with multiple host species. Am Nat. 2004; 164(S5): S64-S78. DOI: 10.1086/424681
60. Calisher CH, Childs JE, Field HE, Holmes KV, and Schountz T. Bats: Important reservoir hosts of emerging viruses. Clin Microbiol Rev. 2006; 19(3): 531-545. DOI: 10.1128/CMR.00017-06
61. Dietrich M, Gómez-Díaz E, and McCoy KD. Worldwide distribution and diversity of seabird ticks: Implications for the ecology and epidemiology of tick-borne pathogens. Vector Borne Zoonotic Dis. 2011; 11(5): 453-470. DOI: 10.1089/vbz.2010.0009
62. Viana M, Mancy R, Biek R, Cleaveland S, Cross PC, Lloyd-Smith JO, et al. Assembling evidence for identifying reservoirs of infection. Trends Ecol Evol. 2014; 29(5): 270-279. DOI: 10.1016/j.tree.2014.03.002
63. Karesh WB, Dobson A, Lloyd-Smith JO, Lubroth J, Dixon MA, Bennett M, et al. Ecology of zoonoses: Natural and unnatural histories. Lancet. 2012; 380(9857): 1936-1945. DOI: 10.1016/S0140-6736(12)61678-X
64. Pearce-Duvet JM. The origin of human pathogens: Evaluating the role of agriculture and domestic animals in the evolution of human disease. Biol Rev. 2006; 81(3): 369-382. DOI: 10.1017/S1464793106007020
65. Gamble A, Olarte-Castillo XA, and Whittaker GR. Backyard zoonoses: The roles of companion animals and peri-domestic wildlife. Sci Transl Med. 2023; 15(718): eadj0037. DOI: 10.1126/scitranslmed.adj0037
66. Pauciullo S, Zulian V, La Frazia S, Paci P, and Garbuglia AR. Spillover: Mechanisms, genetic barriers, and the role of reservoirs in emerging pathogens. Microorganisms. 2024; 12(11): 2191. DOI: 10.3390/microorganisms12112191
67. Dominguez-Oliva A, Hernández-Ávalos I, Martinez-Burnes J, Olmos-Hernandez A, Verduzco-Mendoza A, and Mota-Rojas D. The importance of animal models in biomedical research: Current insights and applications. Animals. 2023; 13(7): 1223. DOI: 10.3390/ani13071223
68. Silva MJ, Fehrenbach GW, Pogue R, Murray P, Rezoagli E, Laffey JG, et al. Sepsis modelling: Current approaches and organ-on-chip perspectives. EBioMedicine. 2026; 125: 106120. DOI: 10.1016/j.ebiom.2026.106120
69. Sarkar S, and Heise MT. Mouse models as resources for studying infectious diseases. Clin Ther. 2019; 41(10): 1912-1922. DOI: 10.1016/j.clinthera.2019.08.010
70. Chuprin J, Buettner H, Seedhom MO, Greiner DL, Keck JG, Ishikawa F, et al. Humanized mouse models for immuno-oncology research. Nat Rev Clin Oncol. 2023; 20(3): 192-206. DOI: 10.1038/s41571-022-00721-2
71. Park JG, Pino PA, Akhter A, Alvarez X, Torrelles JB, and Martinez-Sobrido L. Animal models of COVID-19: Transgenic mouse model. In: Chu JJH, Ahidjo BA, Mok CK, editors. SARS-CoV-2: Methods and protocols. New York, NY: Springer USA; 2022. p. 259-289. DOI: 10.1007/978-1-0716-2111-0_16
72. Lutz C, Maher L, Lee C, and Kang W. COVID-19 preclinical models: Human angiotensin-converting enzyme 2 transgenic mice. Hum Genomics. 2020; 14(1): 20. DOI: 10.1186/s40246-020-00272-6
73. Miao J, Chard LS, Wang Z, and Wang Y. Syrian hamster as an animal model for the study on infectious diseases. Front Immunol. 2019; 10: 2329. DOI: 10.3389/fimmu.2019.02329
74. Iwatsuki-Horimoto K, Nakajima N, Ichiko Y, Sakai-Tagawa Y, Noda T, Hasegawa H, et al. Syrian hamster as an animal model for the study of human influenza virus infection. J Virol. 2018; 92(4): e01693-17. DOI: 10.1128/JVI.01693-17
75. Gruber AD, Firsching TC, Trimpert J, and Dietert K. Hamster models of COVID-19 pneumonia reviewed: How human can they be?. Vet Pathol. 2022; 59(4): 528-545. DOI: 10.1177/03009858211057197
76. Kane Y, Wong G, and Gao GF. Animal models, zoonotic reservoirs, and cross-species transmission of emerging human-infecting coronaviruses. Annu Rev Anim Biosci. 2023; 11(1): 1-31. DOI: 10.1146/annurev-animal-020420-025011
77. Pramod RK, Atul PK, Pandey M, Anbazhagan S, Mhaske ST, and Barathidasan R. Care, management, and use of ferrets in biomedical research. Lab Anim Res. 2024; 40(1): 10. DOI: 10.1186/s42826-024-00197-4
78. Smith RE, Choudhary S, and Ramirez JA. Ferrets as models for viral respiratory disease. Comp Med. 2023; 73(3): 187-193. DOI: 10.30802/AALAS-CM-22-000109
79. Buela L, Cuenca M, Sarmiento J, Peláez D, Mendoza AY, Cabrera EJ, et al. Role of guinea pigs (*Cavia porcellus*) raised as livestock in Ecuadorian Andes as reservoirs of zoonotic yeasts. Animals. 2022; 12(24): 3449. DOI: 10.3390/ani12243449
80. Hensel ME, and Arenas-Gamboa AM. A neglected animal model for a neglected disease: Guinea pigs and the search for an improved animal model for human brucellosis. Front Microbiol. 2018; 9: 2593. DOI: 10.3389/fmicb.2018.02593
81. Yadav SK, Tabassum M, Yadav S, and Ahaduzzaman M. Evaluation of injectable anaesthetic drugs during spaying in rabbits. J Lab Anim Res. 2025; 4(6): 63-66. DOI: 10.58803/jlar.v4i6.85
82. Esteves PJ, Abrantes J, Baldauf HM, BenMohamed L, Chen Y, Christensen N, et al. The wide utility of rabbits as models of human diseases. Exp Mol Med. 2018; 50(5): 1-10. DOI: 10.1038/s12276-018-0094-1
83. Moshaveri A, Babazadeh D, Modarresi-Ghazani F, Hejazi V, Saeed M, and Ahmadi Simab P. The effect of topical nitroglycerin on wound healing in rabbits using histopathological investigation. J Vet Physiol

Pathol. 2022; 1(1): 10-16. DOI: 10.58803/jvpp.v1i1.7
84. Peng X, Knouse JA, and Hernon KM. Rabbit models for studying human infectious diseases. Comp Med. 2015; 65(6): 499-508. Available at: https://pubmed.ncbi.nlm.nih.gov/26678367/
85. Suckow MA, Stevens KA, and Wilson RP, editors. The laboratory rabbit, guinea pig, hamster, and other rodents. Academic Press, 2011. Available at: https://books.google.com/books/about/The_Laboratory_Rabbit_Guinea_Pig_Hamster.html?id=HhEs-xsYp6IC
86. Burgos-Rodriguez AG. Zoonotic diseases of primates. Vet Clin North Am Exot Anim Pract. 2011; 14(3): 557-575. DOI: 10.1016/j.cvex.2011.05.006
87. Kwon T. Utilizing non-human primate models to combat recent COVID-19/SARS-CoV-2 and viral infectious disease outbreaks. J Med Primatol. 2024; 53(1): e12689. DOI: 10.1111/jmp.12689
88. Vashishat A, Patel P, Das Gupta G, and Das Kurmi B. Alternatives of animal models for biomedical research: A comprehensive review of modern approaches. Stem Cell Rev Rep. 2024; 20(4): 881-899. DOI: 10.1007/s12015-024-10701-x
89. Steiner N, Brezzina T, Felmy F, Kiene F, Silberstein Y, Ciurkiewicz M, et al. Clinical pathology of renal amyloidosis in a captive population of tree shrews (*Tupaia belangeri*). J Lab Anim Res. 2026; 5(1): 1-14. DOI: 10.58803/jlar.v5i1.88
90. Wen X, Mo S, Chen S, Yu G, Gao L, Chen S, et al. Pathogenic difference of respiratory syncytial virus infection in cotton rats of different ages. Microb Pathog. 2019; 137: 103749. DOI: 10.1016/j.micpath.2019.103749
91. Brüssow H. From bat to worse: The pivotal role of bats for viral zoonosis. Microb Biotechnol. 2025; 18(7): e70190. DOI: 10.1111/1751-7915.70190
92. Siddiqui S, Siddiqui H, Riguene E, and Nomikos M. Zebrafish: A versatile and powerful model for biomedical research. BioEssays. 2025; 47(12): e70080. DOI: 10.1002/bies.70080
93. Morrison TE, and Diamond MS. Animal models of Zika virus infection, pathogenesis, and immunity. J Virol. 2017; 91(8): e00009-17. DOI: 10.1128/JVI.00009-17
94. Zhang B, Duan Z, and Zhao Y. Mouse models with human immunity and their application in biomedical research. J Cell Mol Med. 2009; 13(6): 1043-1058. DOI: 10.1111/j.1582-4934.2008.00347.x
95. Schäfer A, Leist SR, Powers JM, and Baric RS. Animal models of long COVID: A hit-and-run disease. Sci Transl Med. 2024; 16(773): eado2104. DOI: 10.1126/scitranslmed.ado2104
96. Vella R, Panci D, Carini F, Malta G, Vieni S, David S, et al. Cytokines in sepsis: A critical review of the literature on systemic inflammation and multiple organ dysfunction. Front Immunol. 2025; 16: 1682306. DOI: 10.3389/fimmu.2025.1682306
97. Nogueira A, Pires MJ, and Oliveira PA. Pathophysiological mechanisms of renal fibrosis: A review of animal models and therapeutic strategies. *In Vivo*. 2017; 31(1): 1-22. DOI: 10.21873/invivo.11019
98. Dominguez-Oliva A, Hernández-Ávalos I, Martinez-Burnes J, Olmos-Hernandez A, Verduzco-Mendoza A, and Mota-Rojas D. The importance of animal models in biomedical research: Current insights and applications. Animals. 2023; 13(7): 1223. DOI: 10.3390/ani13071223
99. Baric TJ, and Reneer ZB. Animal models, therapeutics, and vaccine approaches to emerging and re-emerging flaviviruses. Viruses. 2024; 17(1): 1. DOI: 10.3390/v17010001
100. Burton DR. Antiviral neutralizing antibodies: From *in vitro* to *in vivo* activity. Nat Rev Immunol. 2023; 23(11): 720-734. DOI: 10.1038/s41577-023-00858-w
101. Lotfalizadeh N, Sadr S, Ahmadi Simab P, Hajjafari A, Borji H, and Bayat Z. CRISPR/Cas9-mediated genome editing: *In vivo* review. J Lab Anim Res. 2022; 1(1): 47-51. DOI: 10.58803/jlar.v1i1.13
102. Erkyihun GA, and Alemayehu MB. One Health approach for the control of zoonotic diseases. Zoonoses. 2022; 2(1): 1-11. DOI: 10.15212/ZOONOSES-2022-0037
103. Singh S, Sharma P, Pal N, Sarma DK, Tiwari R, and Kumar M. Holistic One Health surveillance framework: Synergizing environmental, animal, and human determinants for enhanced infectious disease management. ACS Infect Dis. 2024; 10(3): 808-826. DOI: 10.1021/acsinfecdis.3c00625
104. Carpenter A, Waltenburg MA, Hall A, Kile J, Killerby M, Knust B, et al. Vaccine preventable zoonotic diseases: Challenges and opportunities for public health progress. Vaccines. 2022; 10(7): 993. DOI: 10.3390/vaccines10070993
105. Jimenez CE, Keestra S, Tandon P, Cumming O, Pickering AJ, Moodley A, et al. Biosecurity and water, sanitation, and hygiene (WASH) interventions in animal agricultural settings for reducing infection burden, antibiotic use, and antibiotic resistance: A One Health systematic review. Lancet Planet Health. 2023; 7(5): e418-e434. DOI: 10.1016/S2542-5196(23)00049-9